

## **EXHIBIT C4**

2d ET Sm of June 28 to Jan 2  
 Cas 8 activation

RYT

		vol	Y	10Y
SK2N	.166 (5X)	30	.25	39 30
SK1E	.253 (5X)	30	.66	15.3 11.8
SK36	.141 .142 (5X)	60	.17	5.8 6.5
SK40	.234 (5X)	30	.57	17.6 13.6
SK42	.235 (5X)	30	.57	17.5 13.6

(A) Lo PH,  
 no DIT, 15"

- RIPA/NP/DC  
 15", no DIT

(SNAP PROTEIN)

CL2N	.328 (5X)	.125 (5X)	.07	$\boxed{29X} = 1.75X$
CL2E	.329 (5X)	.135 (5X)	.11	$\boxed{29X} = 15.9X = 1.75X$

PM

SK2N	.332 (2X)	2.5	3.9
SK1E	.450 (2X)	3.9	8.6
SK36	.191 (2X)	.92	10.8
SK40	.404 (2X)	3.4	3.0
SK42	.571 (2X)	3	3.3

CL2N	.328 (5X)	1.0	10
CL2E	.329 (5X)	1.0	10

Ge1 (3) Cas 8 PM 10X

(M) SK2N	1E	36	40	42	(M) CL2N	CL2E (M)
(1:2) 7.8	5.2	21.6	6	6.6	20	20

Ge1C4 Cas 8 Cyt 10X SK, 1.75X CL

SK2N	1E	36	40	42	(M) CL2N	CL2E
(1:2) 46.8	18.4	69.6	21.1	21	(1:2) 3.5	3.5
20	50	50	50	50		

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## Results

At 36 hrs processing of Figure 8 is seen in melanoma cells

Cyt fraction  $\left[ \begin{array}{l} - \sim 43 \text{ kD} \\ - 24 \text{ kD} \text{ * also appears @ } 42 \text{ hrs but not } 40 \text{ hrs} \\ - \sim 20 \text{ kD} \\ - \sim 18 \text{ kD} \end{array} \right.$

In addition a large band  $\sim 90 \text{ kD}$  is induced @ the plasma membrane, the 24 kD fragment is added in in fraction

- No active S processing seen in melanocytes

## Results

- ET-1 activates active S transiently 36 hrs seems maximal though hasn't peaked at time points between 24 & 36 hrs

- Kinetics of activation may be different in melanocytes and/or may need to be grown in PDDEV post (the cells were not very healthy and were taken directly from PDDEV).